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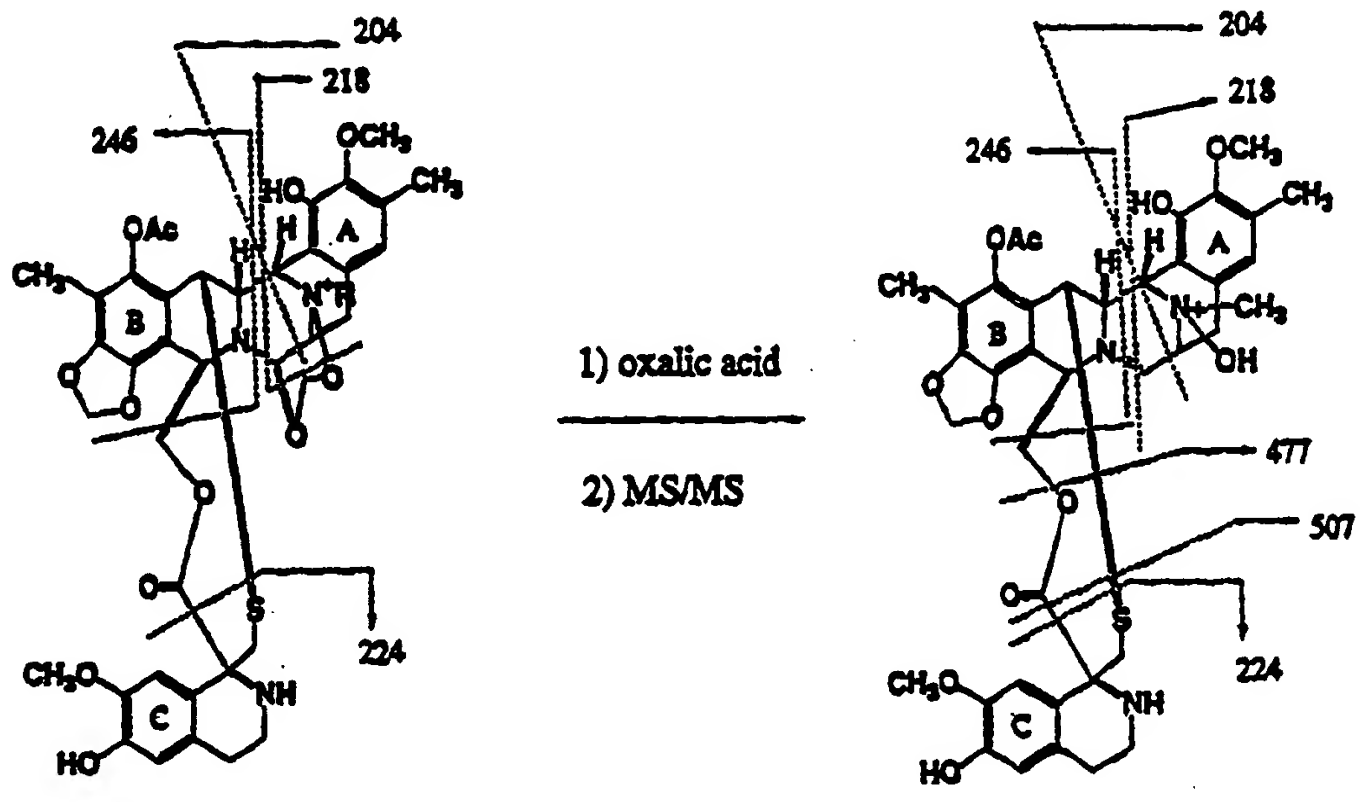
(54) Title: NUCLEOPHILE SUBSTITUTED ECTEINASCIDINS AND N-OXIDE ECTEINASCIDINS



(57) Abstract

Five new nucleophile substituted ecteinascidin (Et) compounds have been isolated from extracts of *Ecteinascidia turbinata*. These compounds have been purified by chromatographic techniques and their structures and bioactivities have been determined. The five nucleophile substituted Et compounds have been designated herein as Et 802 (1), Et 788 (2), Et 760 (3), Et 858 (4) and Et (815) (5). Also obtained were three new N–oxide ecteinascidin compounds, which have been designated herein as Et 717 (6), Et 775 (7) and Et 789 (8). Some of these newly discovered Et compounds show exceedingly potent cytotoxicity against L1210.

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NUCLEOPHILE SUBSTITUTED ECTEINASCIDINS AND N-OXIDE ECTEINASCIDINS

BACKGROUND OF THE INVENTION

Ecteinascidins (Ets), exceedingly potent antitumor agents, first isolated from the marine tunicate *Ecteinascidia turbinata*, especially Et 743, Et 729, Et 746 and Et 722 show significant efficacy *in vivo* against tumor cell lines including P388 murine leukemia, B16 melanoma, Lewis lung carcinoma, and human tumor xenograft models in mice.

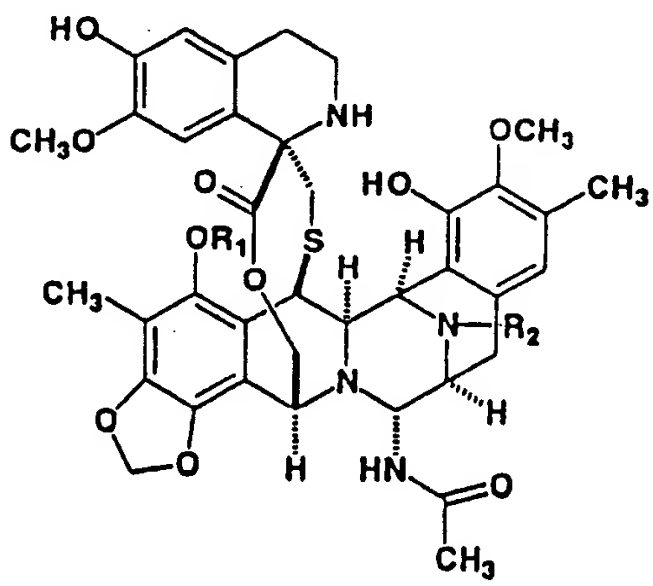
Continuing studies by Rinehart et al. are directed variously toward providing adequate quantities of these compounds for clinical trials, study of their antitumor mechanism of action, and determination of structure-activity relationships. In addition, the discovery of additional Et compounds, whether minor natural components or precursor compounds, will not only provide evidence for their biosynthetic pathway, but should also be useful for with respect to determining structure-activity relationships.

SUMMARY OF THE INVENTION

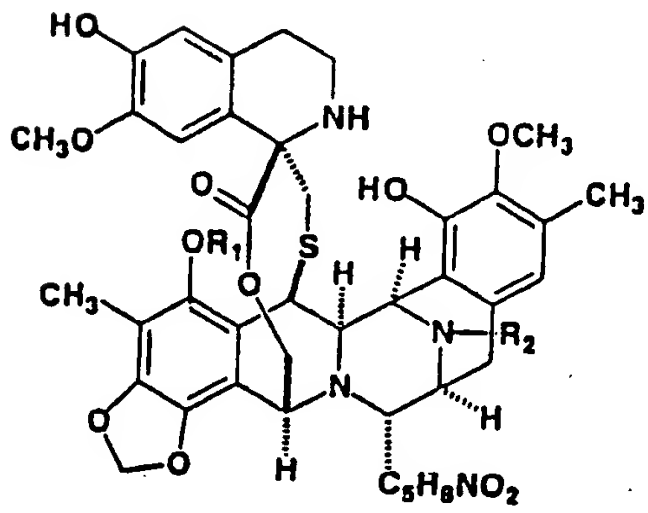
The present invention is directed to several newly discovered ecteinascidin (Et) compounds, all isolated from extracts of *Ecteinascidia turbinata*. For a detailed discussion of previously discovered ecteinascidin compounds, as well as the methods used for their isolation and purification, see

Sakai et al., *J. Amer. Chem. Soc.*, **1996**, *118*, 9017, the disclosure of which is hereby incorporated herein by reference.

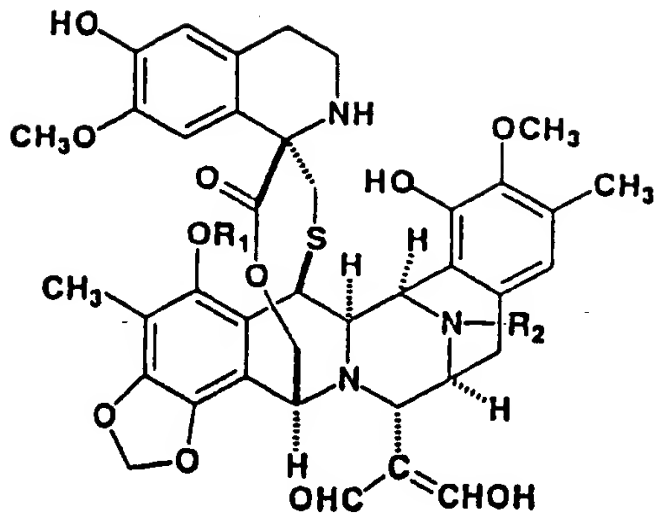
The structures of the new ecteinascidin compounds reported herein are as follows:



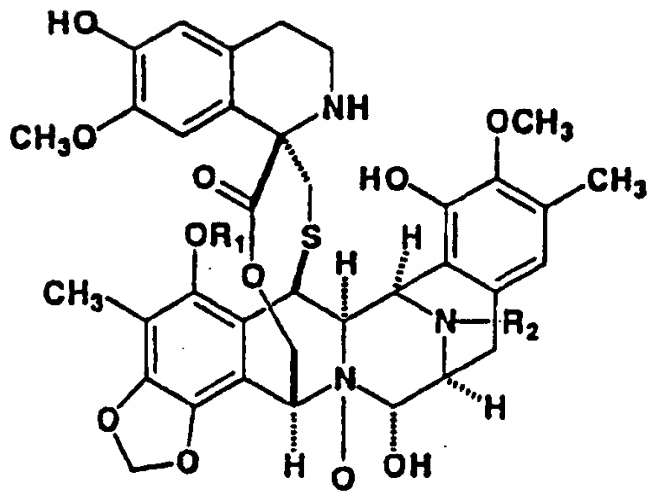
1: ET802, R1=Ac, R2=Me
2: ET760, R1=H, R2=Me
3: ET788, R1=Ac, R2=H



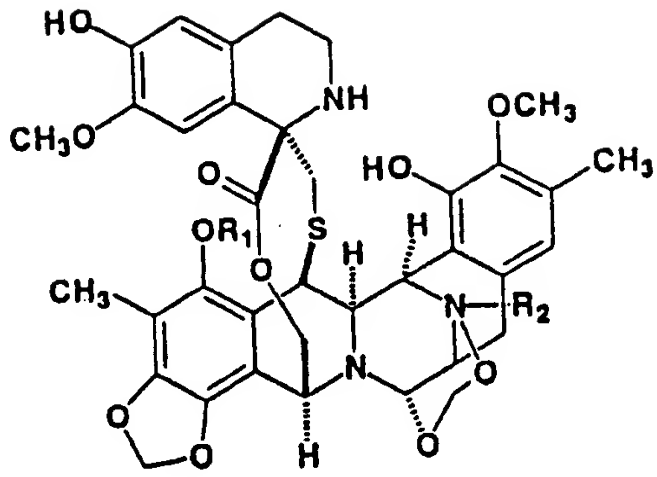
4: ET858 , R1=Ac, R2=Me



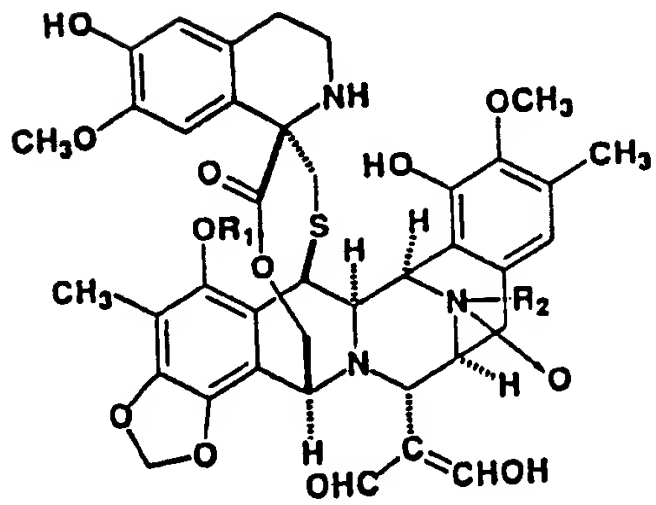
5: ET815, R1=Ac, R2=Me



6: ET717, R1=H, R2=Me



7: ET776, R1=Ac, R2=H
8: ET789, R1=Ac, R2=Me
(fragment ET757)



9: ET832, R1=Ac, R2=Me
(fragment ET 813)

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 illustrates schematically the chromatographic processes used to isolate Et 717, Et 815, Et 813, Et 729 and Et 731 from extracts of *Ecteinascidia turbinata*.

Figure 2 illustrates schematically the chromatographic processes used to isolate Et 729, Et 743, Et 788, Et 757, Et 789, Et 775, Et 745, Et 760, Et 802, Et 858 and Et 745 from extracts of *Ecteinascidia turbinata*.

Figure 3 illustrates schematically the chromatographic processes used to isolate Et 771, Et 759A, Et 743 and Et 729 from extracts of *Ecteinascidia turbinata*.

Figure 4 illustrates the MS/MS fragmentation of Et 802.

Figure 5 illustrates the MS/MS fragmentation of Et 760.

Figure 6 illustrates the MS/MS fragmentation of Et 788.

Figure 7A illustrates the MS/MS fragmentation of Et 858 and Figure 7B illustrates the MS/MS fragmentation of the fragment ion (m/z 800) thereof.

Figure 8 illustrates the MS/MS fragmentation of Et 717.

Figure 9A illustrates the MS/MS fragmentation of Et 789 (8, R = CH_3) and Et 775 (7, R = H) and Figure 9B illustrates the MS/MS fragmentation of the reaction product of Et 789 treated with oxalic acid.

DETAILED DESCRIPTION OF THE INVENTION

The five new nucleophile substituted ecteinascidin compounds, designated herein as Et 802 (1), Et 788 (2), Et 760 (3), Et 858 (4), Et 815 (5) and three new N-oxide ecteinascidins, designated herein as Et 717 (6), Et 775 (7) and Et 789 (8) were isolated and purified from extracts of *Ecteinascidia turbinata* by CCC, NP and RP column chromatography and RP-C18 HPLC as described in Figures 1-3.

The structures of the new Et compounds were assigned based on mass spectral data (HRFABMS, MS/MS fragmentation) and detailed analysis of 1D and 2D-NMR spectral data. Figures 4-9 illustrate MS/MS fragmentation for Et 802, Et 760, Et 788, Et 858, Et 717 and Et 789, respectively.

Spectral data for some of the new ecteinascidin compounds include the following:

Et 802 (1): HRFABMS: *m/z* 803.2962, M+H ion, $C_{41}H_{47}N_4O_{11}S$, Δ = 3.1 mDa; ^{1}H NMR, δ 4.15 (d, 1, H-1), 3.45 (br.d, H-3), 4.50 (br, H-4), 4.19 (dd, 1,2, H11), 3.09 (d, 12, H13), 2.98 (d, 15, H14a), 2.81 (dd, 12, 15, H14b), 6.46 (s, H15), 5.08 (dd, 2, 8, H21), 5.24 (d, 11, H22a), 4.01 (dd, 1, 11, H22b), 3.18 (ddd, H3'a), 2.78 (ddd, H3'b), 2.58 (ddd, H4'a), 2.30 (ddd, H4'b), 6.46 (s, H5'), 6.36 (s, H8'), 2.24 (d, 12, H12'a), 1.93 (d, 12, H12'b), 6.09 (s, -OCH_2O-), 6.03 (s, -OCH_2O-), 3.52 (s, 7'OMe), 3.66 (s, 17OMe), 2.25 (s, AcMe), 2.07 (s, NMe), 2.24 (s, 16Me), 1.96 (s, 6Me), 2.03 (s, NHCOMe).

Et 788 (2): HRFABMS: *m/z* 789.2806, M+H ion, $C_{40}H_{45}N_4O_{11}S$, Δ = 1.0 mDa; ^{1}H NMR, δ 4.21 (d, 1, H-1), 3.45 (br.d, H-3), 4.50 (br, H-4), 4.24 (dd, 1,2, H11), 3.09 (d, 12, H13), 6.48 (s, H15), 5.11 (dd, 2, 8, H21), 5.30 (d, 11, H22a), 4.01 (dd, 1, 11, H22b), 6.48 (s, H5'), 6.39 (s, H8'), 6.13 (s, -OCH_2O-), 6.07 (s, -

OCH_2O-), 3.56 (s, 7'OMe), 3.67 (s, 17OMe), 2.25 (s, AcMe), 2.24 (s, 16Me), 1.96 (s, 6Me), 2.03 (s, NHCOMe).

Et 760 (3): HRFABMS: *m/z* 761.2856, M+H ion, $C_{39}H_{45}N_4O_{10}S$, Δ = 0.2 mDa; ^1H NMR, δ 4.15 (d, 1, H-1), 3.56 (br.d, H-3), 4.50 (br, H-4), 4.32 (dd, 1,2, H11), 3.09 (d, 12, H13), 3.00 (d, 15, H14a), 2.86 (dd, 12, 15, H14b), 6.52 (s, H15), 5.11 (dd, 2, 8, H21), 5.20 (d, 11, H22a), 4.01 (dd, 1, 11, H22b), 3.18 (ddd, H3'a), 2.78 (ddd, H3'b), 2.58 (ddd, H4'a), 2.30 (ddd, H4'b), 6.38 (s, H5'), 6.34 (s, H8'), 2.24 (d, 12, H12'a), 2.03 (d, 12, H12'b), 5.98 (s, -OCH_2O-), 5.85 (s, -OCH_2O-), 3.54 (s, 7'OMe), 3.74 (s, 17OMe), 2.13 (s, NMe), 2.29 (s, 16Me), 2.06 (s, 6Me), 2.12 (s, NHCOMe).

Et 858 (4): HRFABMS: *m/z* 859.3192, M+H ion, $C_{44}H_{51}N_4O_{12}S$, Δ = 3.2 mDa; fragment ion *m/z* 800: *m/z* 800.2825, M+H ion, $C_{42}H_{46}N_3O_{11}S$, Δ = 2.8 mDa; Et 858, ^1H NMR, δ 4.13 (br.s, H-1), 3.41 (br.d, H-3), 4.50 (br, H-4), 4.36 (d, 3, H11), 2.79 (d, 13, H13), 3.01 (d, 12, H14a), 2.88 (dd, 12, 13, H14b), 6.50 (s, H15), 5.10 (d, 2, H21), 5.28 (d, 11, H22a), 4.09 (dd, 1.5, 11, H22b), 3.18 (ddd, H3'a), 2.62 (ddd, H3'b), 2.53 (ddd, H4'a), 2.45 (ddd, H4'b), 6.43 (s, H5'), 6.38 (s, H8'), 2.25 (d, 12, H12'a), 2.14 (d, 12, H12'b), 6.08 (s, -OCH_2O-), 5.98 (s, -OCH_2O-), 3.57 (s, 7'OMe), 3.73 (s, 17OMe), 2.28 (s, AcMe), 2.27 (s, 16Me), 2.01 (s, 6Me), 2.15 (s, NHCOMe), 2.09 (s, NHCOMe), 3.25 (NHCOMe), 2.64 (m, NHCOMe).

Et 717 (6): HRFABMS: *m/z* 718.2435, M+H ion, $C_{37}H_{40}N_3O_{10}S$, Δ = -0.1 mDa; ^1H NMR, δ 6.55 (H15), 6.44 (H8'), 6.38 (H5'), 6.07, 5.92 (-OCH_2O-), 5.78, 4.09 (H22a,b), 5.30 (H1), 5.19 (H21), 4.92 (H4), 4.57 (H11), 4.41 (H3), 3.64 (H13), 3.22, 2.91 (H14a,b), 3.00, 2.85 (H3'a,b), 2.61, 2.38 (H4'a,b), 3.74 (17-OCH_3), 3.54 (7'-OCH_3), 2.35 (6-CH_3), 2.27 (16-CH_3), 2.16 (N-CH_3).

Et 775 (7): HRFABMS: *m/z* 776, $C_{39}H_{42}N_3O_{12}S$, Δ = -0.0 mDa.

Et 789 (8): HRFABMS: *m/z* 790, $C_{40}H_{44}N_3O_{12}S$, Δ = -0.2 mDa; 12N-CH_3, δ 2.65 (singlet) observed in ^1H NMR.

Several of these new ecteinascidin compounds show exceedingly potent cytotoxicity against L1210 (see Table 1).

TABLE 1

Et Compound	IC_{50} ng/ml against L1210
Et 802 (1)	7
Et 788 (2)	0.5
Et 760 (3)	32
Et 858 (4)	0.4
Et 815 (5)	0.4

As shown above, the present invention is directed to bioactive compounds. These compounds have been prepared in substantially pure form, i.e., at a purity level sufficient to allow physical and biological characterization thereof. As described above, these compounds have been found to possess specific antitumor activities and as such they will be useful as medicinal agents in mammals, particularly in humans. Thus, another aspect of the present invention concerns pharmaceutical compositions containing the active compounds identified herein and methods of treatment employing such pharmaceutical compositions.

The active compounds of the present invention exhibit antitumor activity. Thus, the present invention also provides a method of treating any mammal affected by a malignant tumor sensitive to these compounds, which comprises administering to the affected individual a therapeutically effective amount of an

active compound or mixture of compounds, or pharmaceutical compositions thereof. The present invention also relates to pharmaceutical preparations, which contain as active ingredient one or more of the compounds of this invention, as well as the processes for its preparation.

Examples of pharmaceutical compositions include any solid (tablets, pills, capsules, granules, etc.) or liquid (solutions, suspensions or emulsions) with suitable composition or oral, topical or parenteral administration, and they may contain the pure compound or in combination with any carrier or other pharmacologically active compounds. These compositions may need to be sterile when administered parenterally.

The correct dosage of a pharmaceutical composition comprising the compounds of this invention will vary according to the particular formulation, the mode of application, and the particular *situs*, host and bacteria or tumor being treated. Other factors like age, body weight, sex, diet, time of administration, rate of excretion, condition of the host, drug combinations, reaction sensitivities and severity of the disease shall be taken into account. Administration can be carried out continuously or periodically within the maximum tolerated dose.

Several known ecteinascidin compounds, including Et 743 and Et 729 were also isolated, as shown below in Table 2.

TABLE 2

Quantities of Et Compounds Isolated

Fraction A (550 mg)		Fraction B (261 mg)		Fraction C (40 mg)	
Et 729	39.4 mg	Et 729	31.6 mg	Et 743	10.2 mg
Et 731	11.1 mg	Et 743	0.9 mg	Et 771	5.8 mg
Et 745	45.4 mg	Et 745	6.0 mg	Et 759A	3.5 mg
Et 759B	46.4 mg	Et 802 (1)	1.4 mg*		
Et 597	3.4 mg	Et 788 (2)	0.2 mg*		
Et 717 (6)	2.6 mg*	Et 760 (3)	1.0 mg*		
Et 815 (5)	5.1 mg*	Et 858 (4)	0.5 mg*		
Et 814 (9)	5.9 mg*	Et 789 (8)	1.5 mg*		
		Et 775 (7)	0.5 mg*		

* - New Ecteinascidin Compounds

The present invention has been described in detail, including the preferred embodiments thereof. However, it will be appreciated that those skilled in the art, upon consideration of the present disclosure, may make modifications and/or improvements on this invention and still be within the scope and spirit of this invention as set forth in the following claims.

CLAIMS:

1. Substantially pure Ecteinascidin 717, free of the cellular debris of *Ecteinascidia turbinata.*

2. Substantially pure Ecteinascidin 815, free of the cellular debris of *Ecteinascidia turbinata.*

3. Substantially pure Ecteinascidin 814, free of the cellular debris of *Ecteinascidia turbinata.*

4. Substantially pure Ecteinascidin 802, free of the cellular debris of *Ecteinascidia turbinata.*

5. Substantially pure Ecteinascidin 788, free of the cellular debris of *Ecteinascidia turbinata.*

6. Substantially pure Ecteinascidin 760, free of the cellular debris of *Ecteinascidia turbinata.*

7. Substantially pure Ecteinascidin 858, free of the cellular debris of *Ecteinascidia turbinata.*

8. Substantially pure Ecteinascidin 789, free of the cellular debris of *Ecteinascidia turbinata.*

9. Substantially pure Ecteinascidin 775, free of the cellular debris of *Ecteinascidia turbinata.*

10. A pharmaceutical or veterinary composition comprising an effective antitumor amount of the substantially pure compound designated

herein as Et 717 and a pharmaceutically acceptable carrier, diluent or excipient.

11. A pharmaceutical or veterinary composition comprising an effective antitumor amount of the substantially pure compound designated herein as Et 815 and a pharmaceutically acceptable carrier, diluent or excipient.

12. A pharmaceutical or veterinary composition comprising an effective antitumor amount of the substantially pure compound designated herein as Et 814 and a pharmaceutically acceptable carrier, diluent or excipient.

13. A pharmaceutical or veterinary composition comprising an effective antitumor amount of the substantially pure compound designated herein as Et 802 and a pharmaceutically acceptable carrier, diluent or excipient.

14. A pharmaceutical or veterinary composition comprising an effective antitumor amount of the substantially pure compound designated herein as Et 788 and a pharmaceutically acceptable carrier, diluent or excipient.

15. A pharmaceutical or veterinary composition comprising an effective antitumor amount of the substantially pure compound designated herein as Et 760 and a pharmaceutically acceptable carrier, diluent or excipient.

16. A pharmaceutical or veterinary composition comprising an effective antitumor amount of the substantially pure compound designated

herein as Et 858 and a pharmaceutically acceptable carrier, diluent or excipient.

17. A pharmaceutical or veterinary composition comprising an effective antitumor amount of the substantially pure compound designated herein as Et 789 and a pharmaceutically acceptable carrier, diluent or excipient.

18. A pharmaceutical or veterinary composition comprising an effective antitumor amount of the substantially pure compound designated herein as Et 775 and a pharmaceutically acceptable carrier, diluent or excipient.

19. The use for the manufacture of a medicament for the therapeutic or prophylactic treatment of a patient suffering from a mammalian tumor, of an effective antitumor amount of the substantially pure compound designated herein as Et 717 and a pharmaceutically acceptable carrier, diluent or excipient.

20. The use for the manufacture of a medicament for the therapeutic or prophylactic treatment of a patient suffering from a mammalian tumor, of an effective antitumor amount of the substantially pure compound designated herein as Et 815 and a pharmaceutically acceptable carrier, diluent or excipient.

21. The use for the manufacture of a medicament for the therapeutic or prophylactic treatment of a patient suffering from a mammalian tumor, of an effective antitumor amount of the substantially pure compound designated herein as Et 814 and a pharmaceutically acceptable carrier, diluent or excipient.

22. The use for the manufacture of a medicament for the therapeutic or prophylactic treatment of a patient suffering from a mammalian tumor, of an effective antitumor amount of the substantially pure compound designated herein as Et 802 and a pharmaceutically acceptable carrier, diluent or excipient.

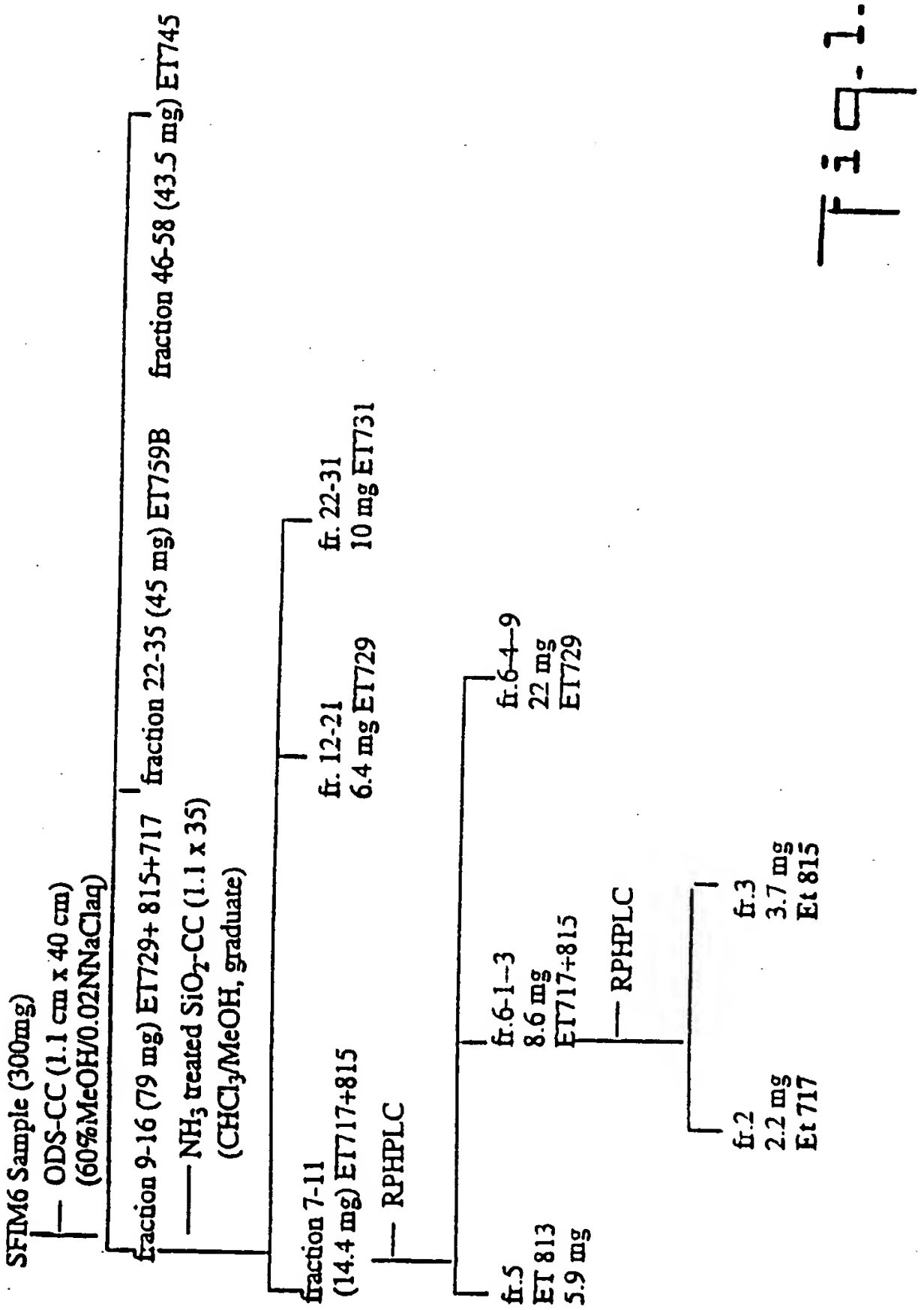
23. The use for the manufacture of a medicament for the therapeutic or prophylactic treatment of a patient suffering from a mammalian tumor, of an effective antitumor amount of the substantially pure compound designated herein as Et 788 and a pharmaceutically acceptable carrier, diluent or excipient.

24. The use for the manufacture of a medicament for the therapeutic or prophylactic treatment of a patient suffering from a mammalian tumor, of an effective antitumor amount of the substantially pure compound designated herein as Et 760 and a pharmaceutically acceptable carrier, diluent or excipient.

25. The use for the manufacture of a medicament for the therapeutic or prophylactic treatment of a patient suffering from a mammalian tumor, of an effective antitumor amount of the substantially pure compound designated herein as Et 858 and a pharmaceutically acceptable carrier, diluent or excipient.

26. The use for the manufacture of a medicament for the therapeutic or prophylactic treatment of a patient suffering from a mammalian tumor, of an effective antitumor amount of the substantially pure compound designated herein as Et 789 and a pharmaceutically acceptable carrier, diluent or excipient.

27. The use for the manufacture of a medicament for the therapeutic or prophylactic treatment of a patient suffering from a mammalian tumor, of an effective antitumor amount of the substantially pure compound designated herein as Et 775 and a pharmaceutically acceptable carrier, diluent or excipient.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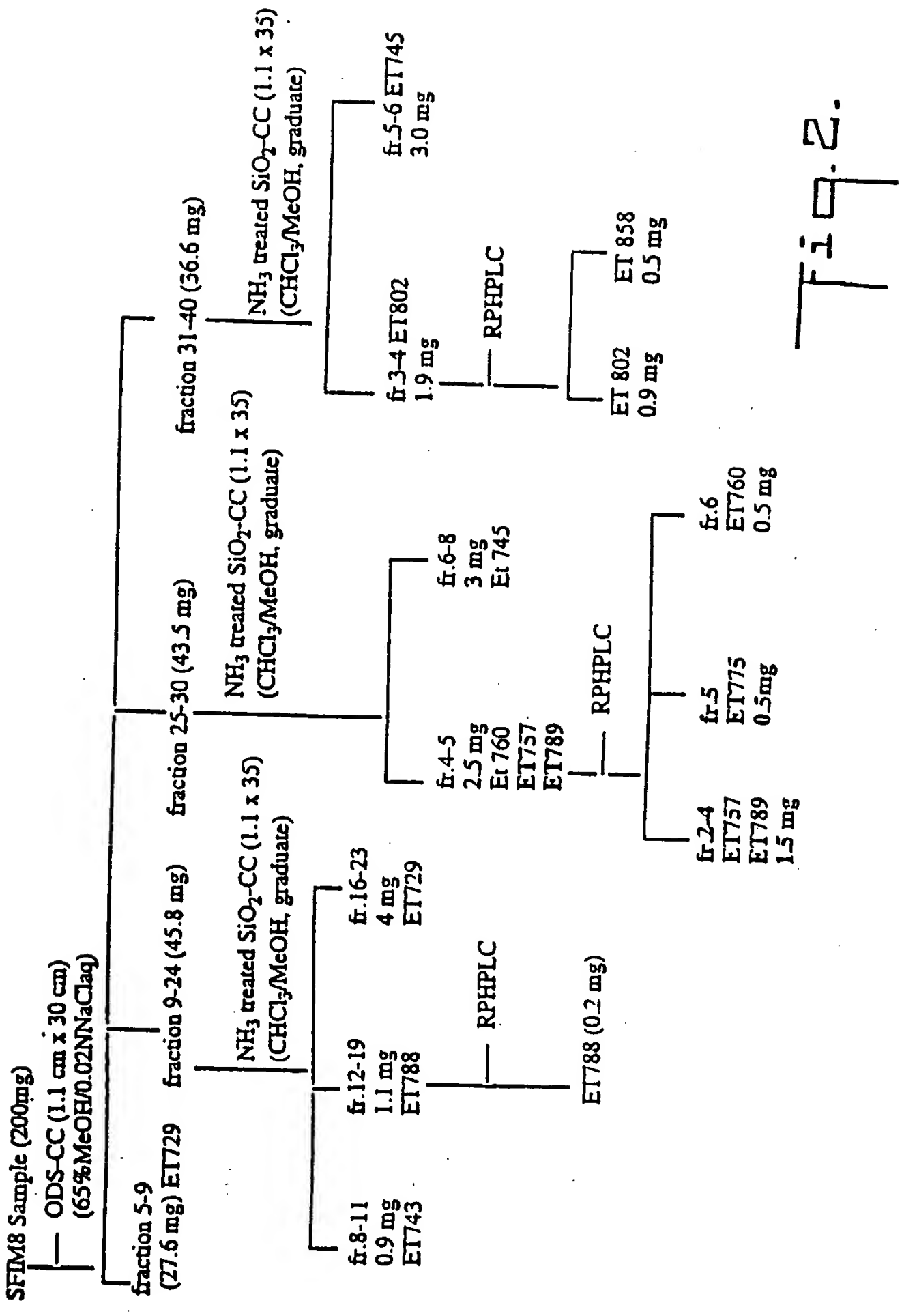
fraction 22-35 (45 mg) ET759B
fraction 46-58 (43.5 mg) ET745
NH3 treated SiO2-CC (1.1 x 35)
(CHCl3/MeOH, graduate)
fraction 7-11
(14.4 mg) ET717+815
fr. 12-21
6.4 mg ET729
fr. 22-31
10 mg ET731
RPHPLC
fr.5
ET 813
5.9 mg
fr.6-1-3
8.6 mg
ET717+815
fr.6-4-9
22 mg
ET729
RPHPLC
fr.2
2.2 mg
Et 717
fr.3
3.7 mg
Et 815

Fig. 1.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ODS-CC (1.1 cm x 30 cm)
(65%MeOH/0.02NNaClaq)
fraction 5-9
(27.6 mg) ET729
fraction 9-24 (45.8 mg)
fraction 25-30 (43.5 mg)
fraction 31-40 (36.6 mg)
NH3 treated SiO2-CC (1.1 x 35)
(CHCl3/MeOH, graduate)
fr.8-11
0.9 mg
ET743
fr.12-19
1.1 mg
ET788
fr.16-23
4 mg
ET729
ET788 (0.2 mg)
RPHPLC
fr.4-5
2.5 mg
Et 760
ET757
ET789
fr.6-8
3 mg
Et 745
fr.3-4 ET802
1.9 mg
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ET 802
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ET 858
0.5 mg
fr.6
ET760
0.5 mg
fr-2-4
ET757
ET789
1.5 mg
fr-5
ET775
0.5mg

Fig. 2.

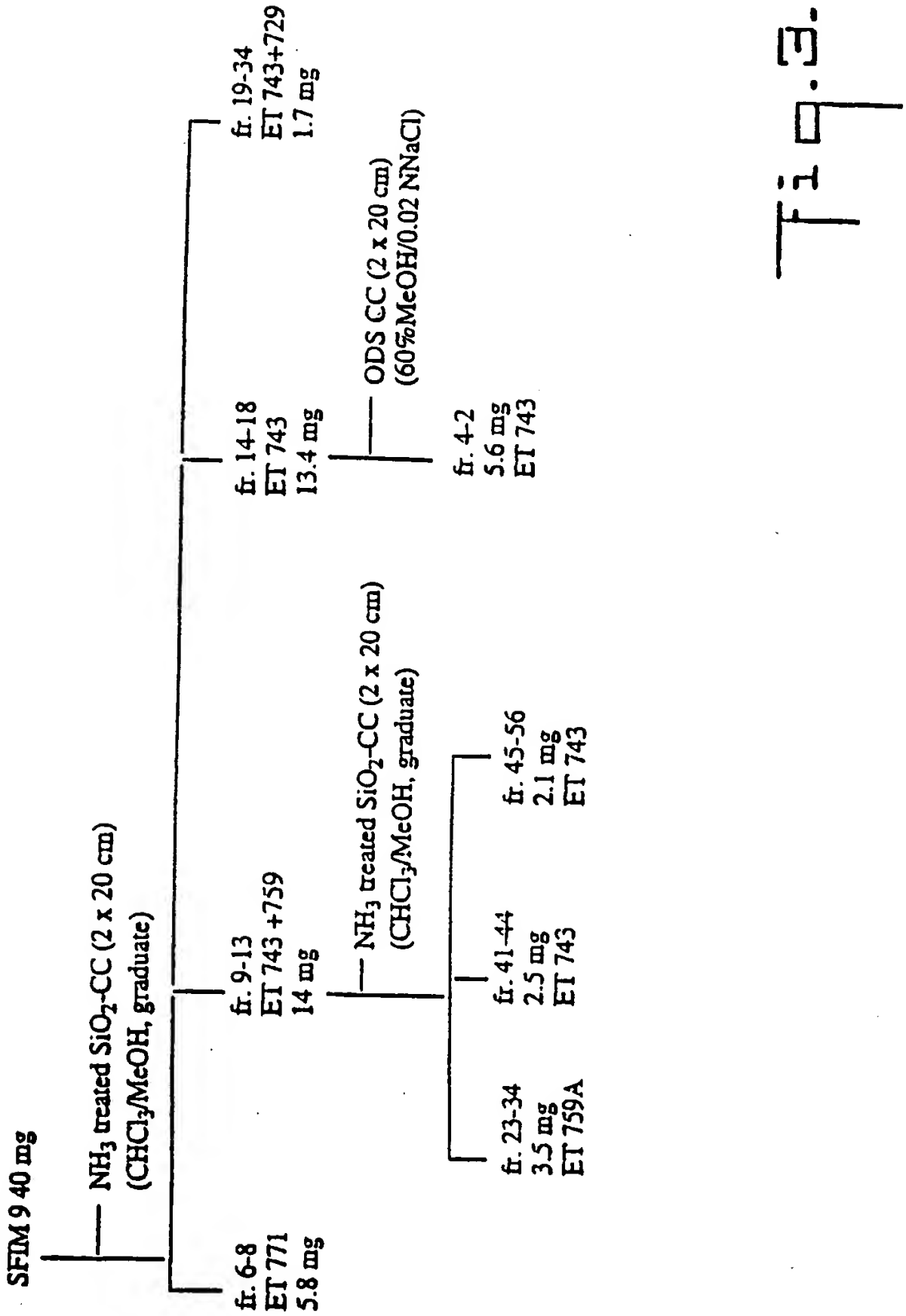
SFIM 9 40 mg
NH3 treated SiO2-CC (2 x 20 cm)
(CHCl3/MeOH, graduate)
fr. 6-8
ET 771
5.8 mg
fr. 9-13
ET 743 +759
14 mg
NH3 treated SiO2-CC (2 x 20 cm)
(CHCl3/MeOH, graduate)
fr. 23-34
3.5 mg
ET 759A
fr. 41-44
2.5 mg
ET 743
fr. 45-56
2.1 mg
ET 743
fr. 14-18
ET 743
13.4 mg
ODS CC (2 x 20 cm)
(60%MeOH/0.02 NNaCl)
fr. 4-2
5.6 mg
ET 743
fr. 19-34
ET 743+729
1.7 mg

Fig. 3.

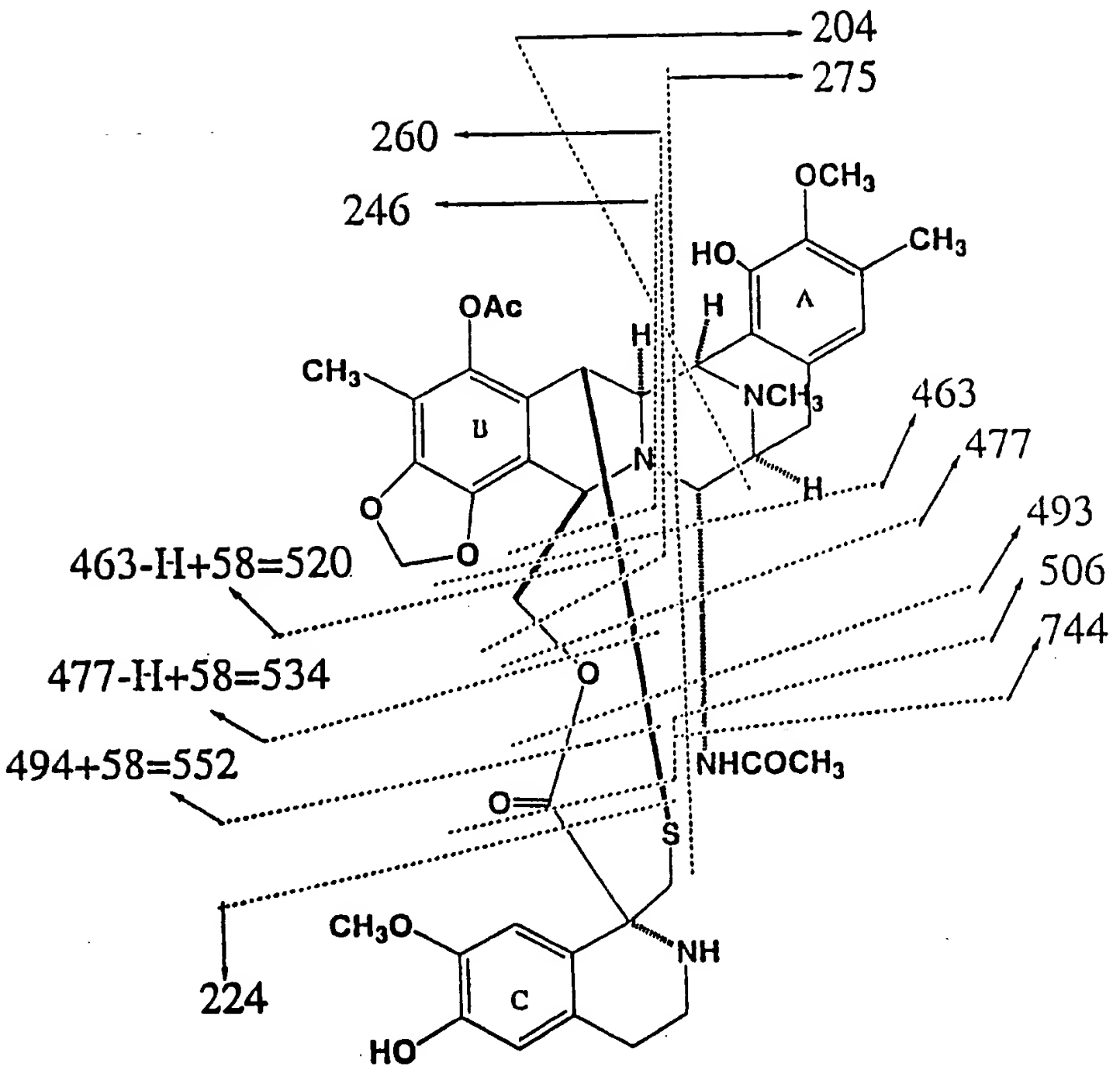
204
275
260
246
OCH3
CH3
HO
H
A
OAc
H
CH3
NCH3
463
477
B
N
H
O
O
493
463-H+58=520
506
744
477-H+58=534
O
494+58=552
NHCOCH3
O
S
CH3O
NH
224
C
HO

Fig.4.

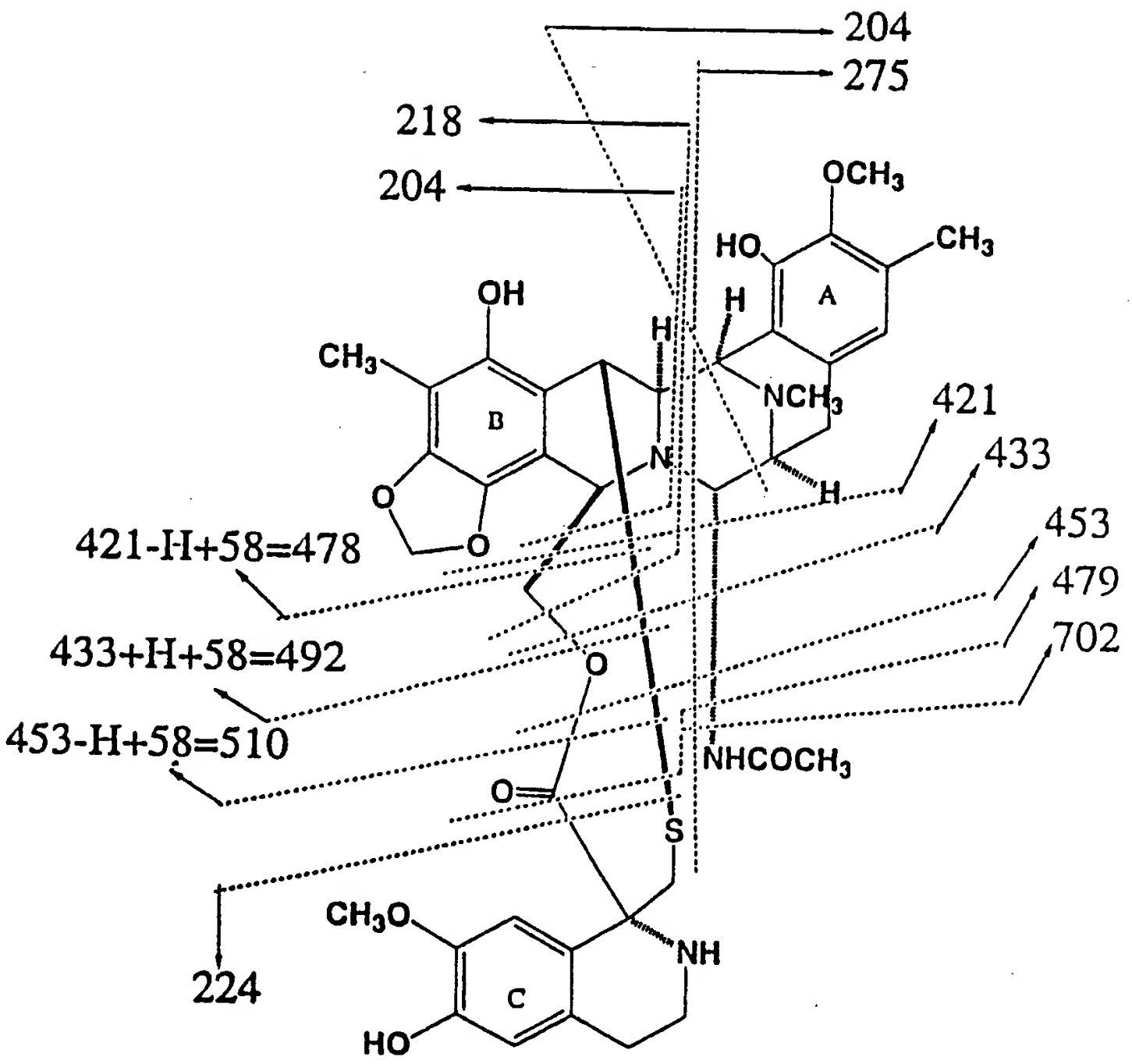
204
275
218
204
OCH3
HO
CH3
A
H
OH
H
CH3
B
NCH3
421
433
N
H
O
O
421-H+58=478
453
479
433+H+58=492
O
702
453-H+58=510
NHCOCH3
O
S
CH3O
NH
224
C
HO

Fig.5.

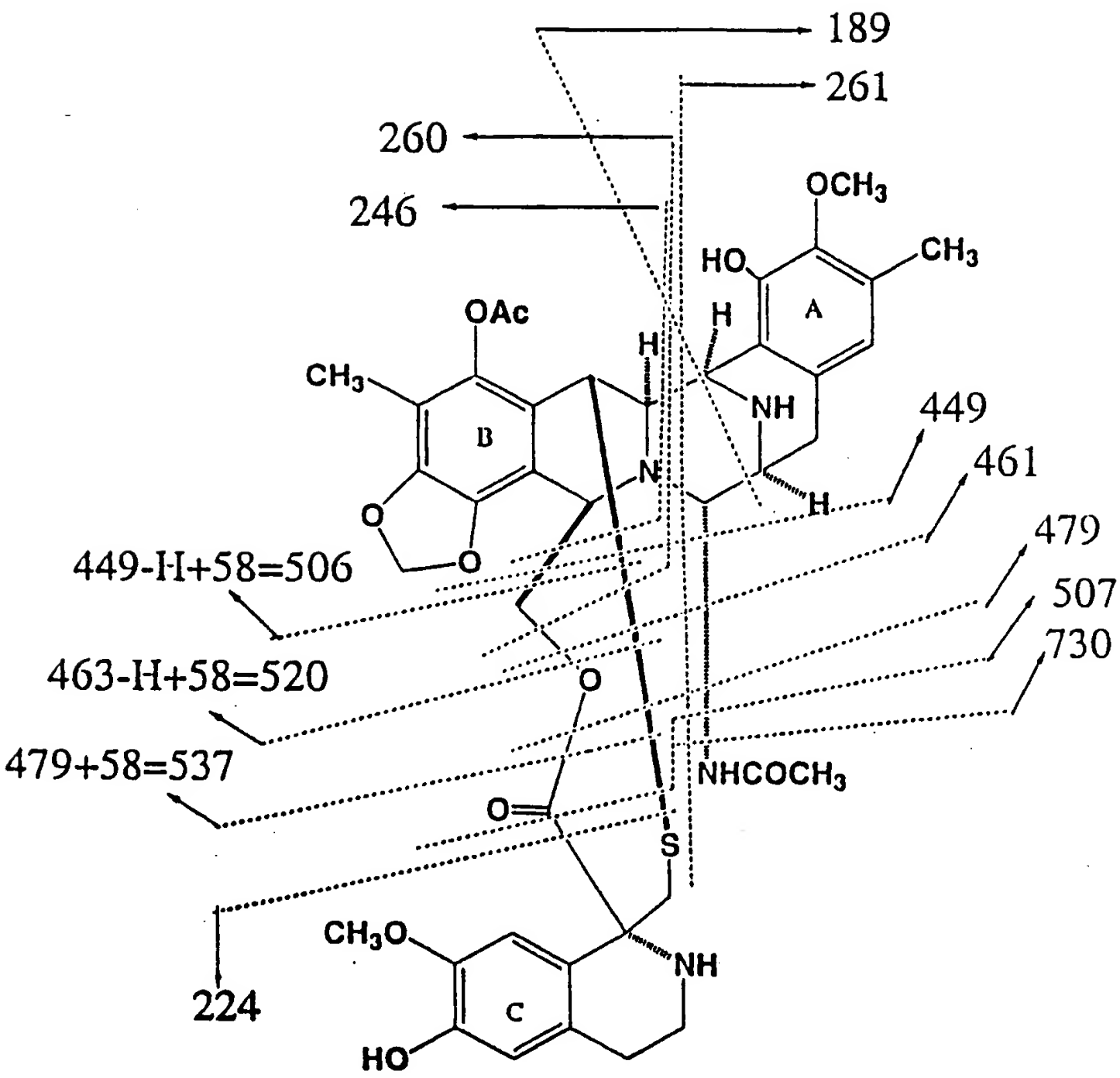
189
261
260
246
OCH3
HO
CH3
A
H
OAc
H
CH3
B
NH
449
461
N
H
O
O
479
449-H+58=506
507
463-H+58=520
730
O
NHCOCH3
479+58=537
O
S
CH3O
NH
224
C
HO

Fig. 6.

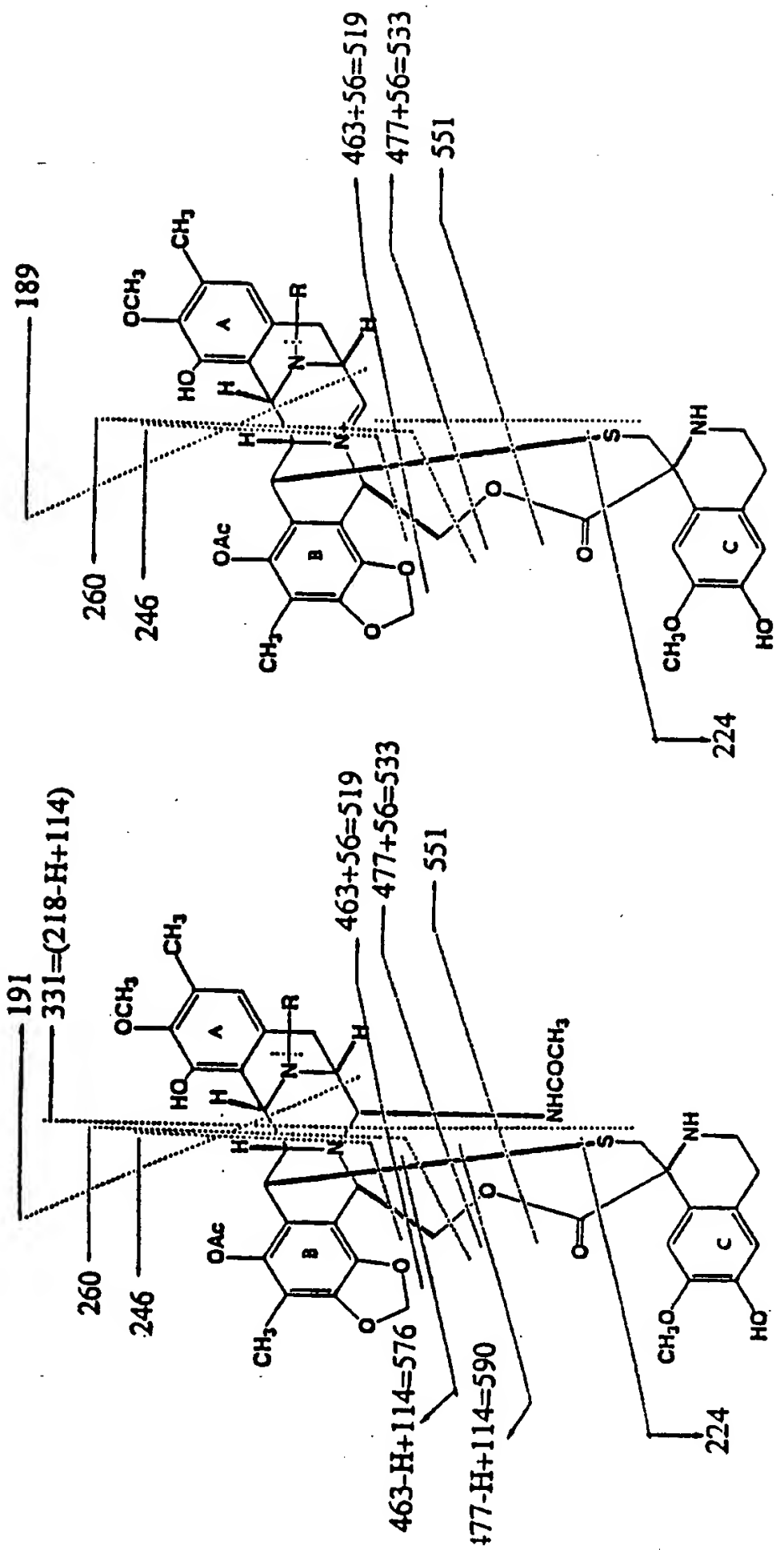
189
260
246
OCH3
CH3
HO
A
R
H
N+
463+56=519
477+56=533
551
OAc
B
O
CH3
S
NH
C
CH3O
HO
224
191
331=(218-H+114)
NHCOCH3
463-H+114=576
477-H+114=590

Fig-7B.

Fig-7A.

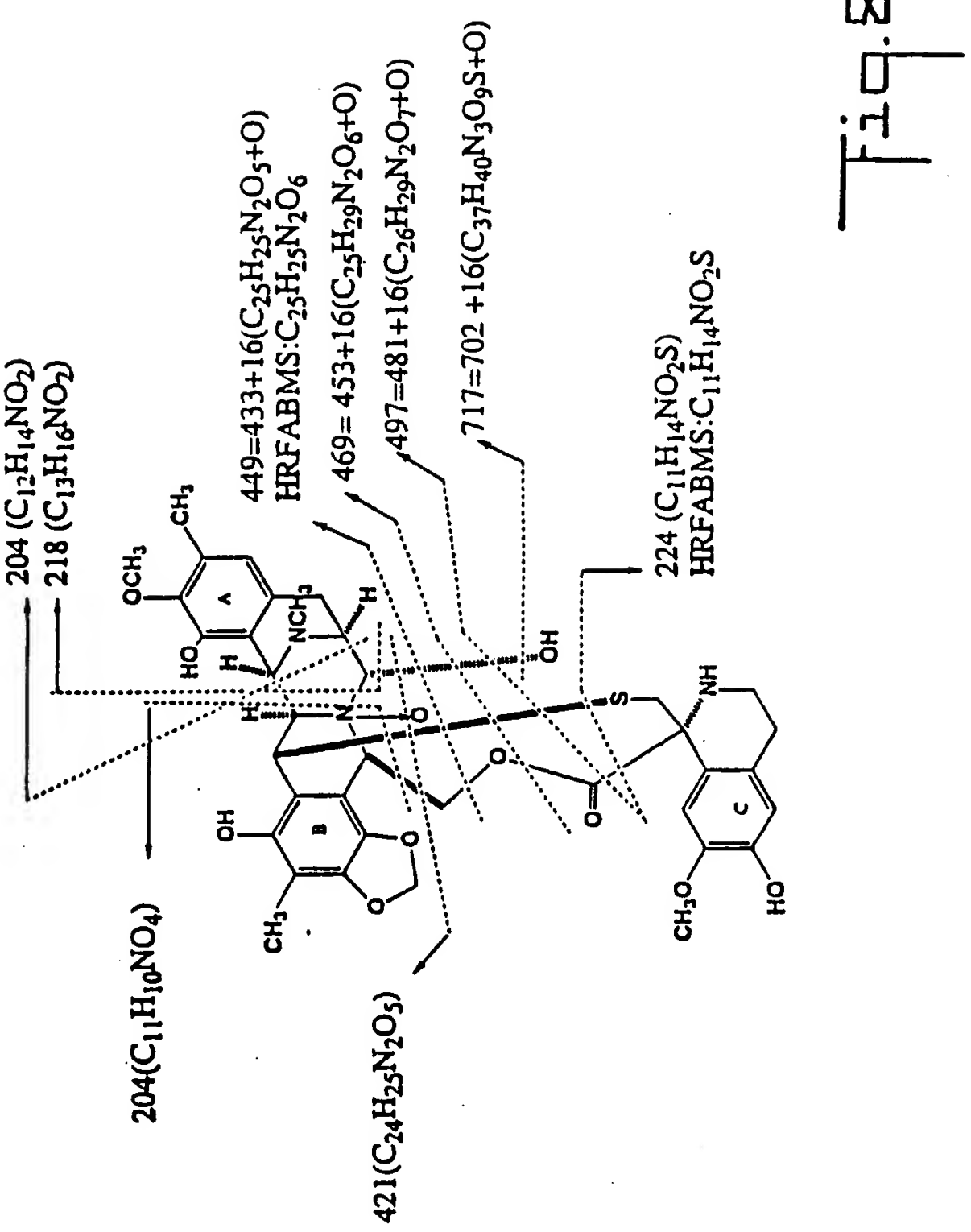
204 ($C_{12}H_{14}NO_2$)
218 ($C_{13}H_{16}NO_2$)
449=433+16($C_{25}H_{25}N_2O_5$+O)
HRFABMS:$C_{25}H_{25}N_2O_6$
469= 453+16($C_{25}H_{29}N_2O_6$+O)
497=481+16($C_{26}H_{29}N_2O_7$+O)
717=702 +16($C_{37}H_{40}N_3O_9S$+O)
224 ($C_{11}H_{14}NO_2S$)
HRFABMS:$C_{11}H_{14}NO_2S$
204($C_{11}H_{10}NO_4$)
421($C_{24}H_{25}N_2O_5$)

Fig. 8

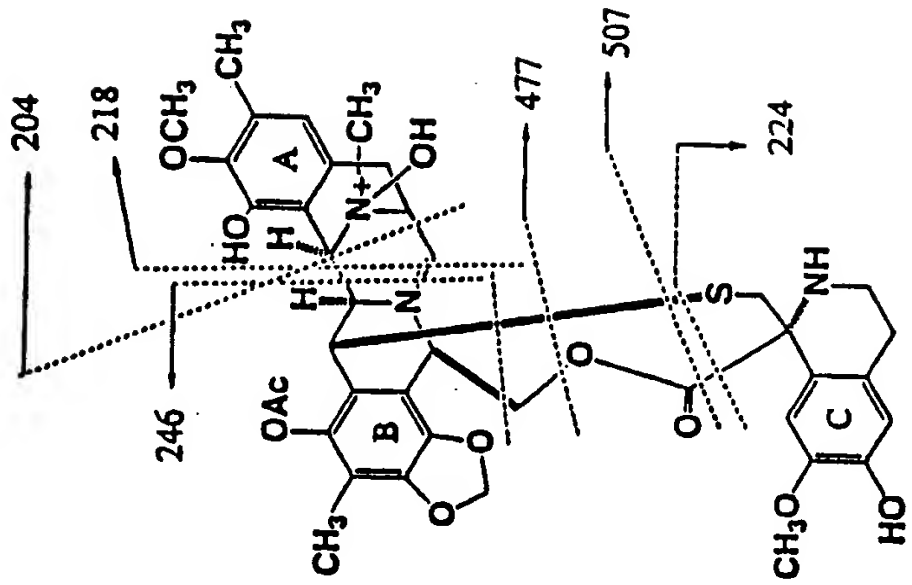

Fig. 9B.

1) oxalic acid

2) MS/MS

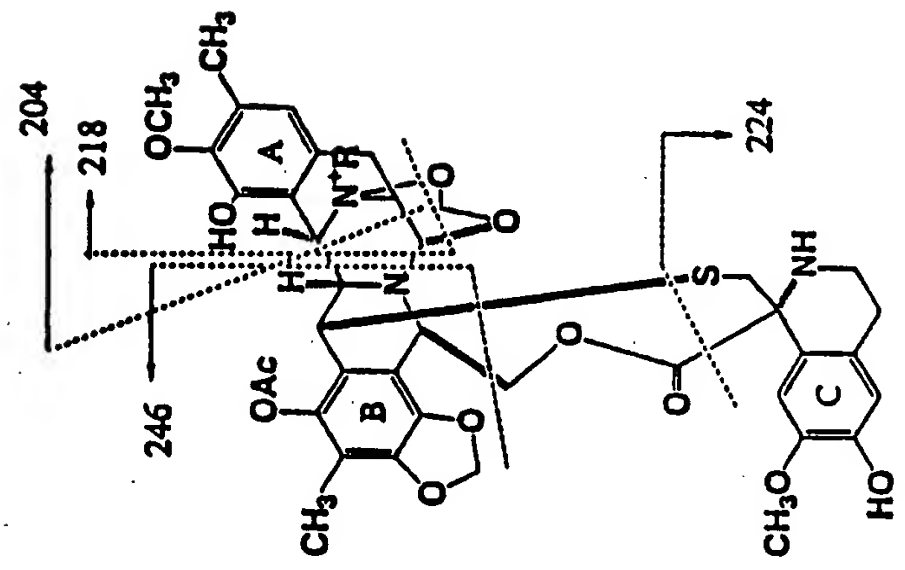

Fig. 9A.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/07340

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A01N 43/58; C07D 237/26, 241/36
US CL :514/250; 544/233, 340

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/250; 544/233, 340

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

NONE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS, CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5,484,717 A (ZACCARDI) 16 January, 1996, col. 1 and 2.	1-27
A	US 5,459,141 A (VERTESY et al) 17 October 1995, abstract and col. 1.	1-27
A	US 4,273,773 A (DEMERSON et al) 16 June 1981, col. 1 and 2.	1-27

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 22 MAY 1998	Date of mailing of the international search report 21 JUL 1998
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer TAMTHOM T. NGO / M. SHAH Telephone No. (703) 308-1235

Form PCT/ISA/210 (second sheet)(July 1992)★